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TETRAHEDRON LETTERS

A *DE NOVO* SYNTHESIS OF ETHYL 2-DEOXY-L-RIBOSIDES[1]

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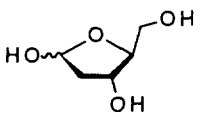
Summary: A short (7-step) and efficient synthesis of several derivatives of 2-deoxy-L-ribose **1**, e.g., the ethyl ribosides, **2abc**, has been accomplished from achiral precursors.

The use of L-enantiomers of natural and modified nucleosides as antiviral agents in medicine has increased dramatically in recent years.[4-8] Several modified nucleosides derived from L-sugars, e. g., L-thymidine (L-T),[5] L-3'-thiacytidine (L-3-TC),[6] L-5-fluoro-3'-thiacytidine (L-FTC),[6a,7] L-2',3'-dideoxycytidine (L-ddC),[8] and L-5-fluoro-2',3'-dideoxycytidine (L-5-FddC),[8b,c] have shown good antiviral activity with greatly reduced toxicity compared to other modified D-nucleosides. In addition, L-nucleosides, either normal (L-RNA) or 2'-deoxy (L-DNA), have been suggested to be of value in antisense oligonucleotide therapy as materials to bind pieces of D-m-RNA.[9] For these reasons, many groups are working on ways to produce modified nucleosides in the unnatural L-configuration, a goal that requires ready access to L-carbohydrates, especially L-ribose and its derivatives. We report herein a short, seven-step synthesis of the α and β-anomers of ethyl 2-deoxy-L-ribofuranoside **2ab** *via* 2-deoxy L-ribose **1**, from the simple achiral material **6**.



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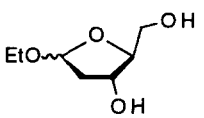
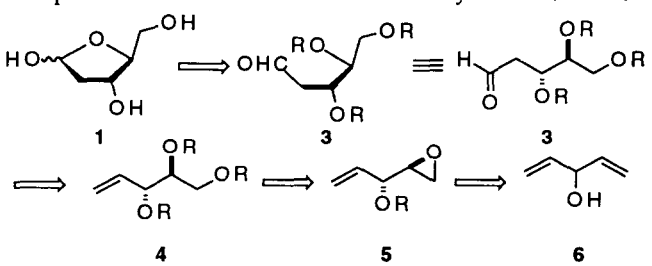


2ab

Several syntheses of 2-deoxy-L-ribose **1** using naturally occurring carbohydrate starting materials such as L-arabinose or L-ascorbic acid have been published.[10] These syntheses have one thing in common: they all begin with L-sugars. Routes have been developed which start with achiral materials,[11] e. g., with 1-(trimethylsilyloxy)butadiene,[12] using a Sharpless asymmetric epoxidation[13] to provide the stereochemistry. Our retrosynthetic analysis (Scheme 1) proposes that 2-deoxy-L-ribose **1** can be derived from the aldehyde **3** with the two stereocenters as shown. The aldehyde of **3** can then be made by oxidation of the alkene in the protected triol **4**, which can in turn be formed from the opening of the epoxide **5** with an oxygen nucleophile at its unsubstituted terminus. Epoxides of this type are made by a Sharpless epoxidation/kinetic resolution of the readily available alcohol **6**.



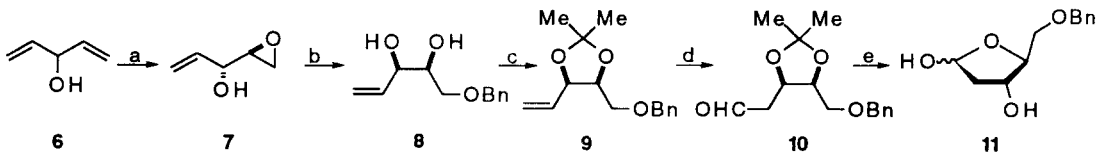
1 **3** **3**

4 **5** **6**

Scheme 1

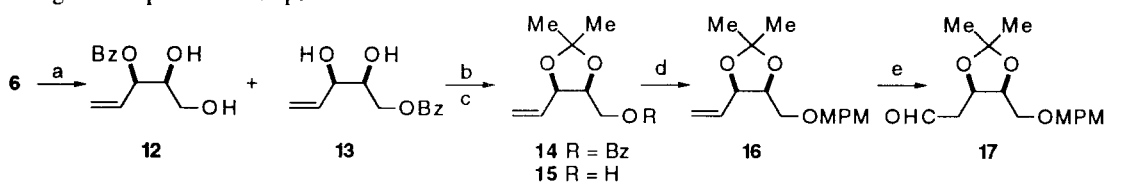
PII: S0040-4039(98)00852-1

Since it had been shown that a regioselective Wacker oxidation[14] could convert an alkene similar to **4** to an aldehyde like **3** in good yield, our first approach began with a synthesis of the acetonide **9**. The epoxy alcohol **7** was made from the alcohol **6**[15] in 62% yield and 100% enantiomeric excess (ee) using D-(-)-isopropyl tartrate under Sharpless epoxidation conditions (Scheme 2).[16] The epoxy alcohol **7** was then dissolved in distilled benzyl alcohol in the presence of $Ti(OiPr)_4$ to give the diol **8** in 60% yield.[17] Treatment of the diol **8** in refluxing acetone with *p*-toluenesulfonic acid and a stoichiometric amount of anhydrous $CuSO_4$ afforded the acetonide **9** in 75% yield. Oxidation of this alkene under Wacker conditions furnished the desired aldehyde **10**, but in only a maximum yield of 38%. Treatment of **10** with aq. HCl gave 5-*O*-benzyl-2-deoxy-L-ribose **11** in 58% yield. Thus this general route is applicable for the synthesis of 2-deoxy-L-ribose derivatives although the overall yield is somewhat low.



Scheme 2. (a) D-(–)-DIPT, $Ti(OiPr)_4$, *t*BuOOH, CH_2Cl_2, 4Å mol. sieves, 62%; (b) BnOH, $Ti(OiPr)_4$, 96 °C, 60%; (c) $(CH_3)_2CO$, $CuSO_4$, TsOH, 75%; (d) $PdCl_2$ (0.2 eq), CuCl, O_2, DMF/H_2O 7:1, 60 °C, 18 h, 38%; (e) HCl (1 M), THF, 58%.

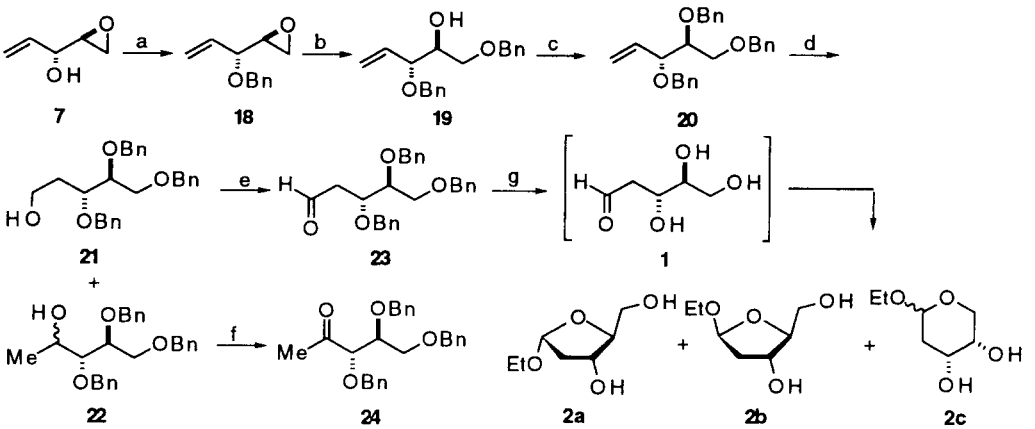
Because of the low yield in the Wacker oxidation step, several minor variations were attempted. Reaction of benzoic acid with the epoxyalcohol **6** gave the isomeric compounds **12** and **13** which were isolated in 19% and 32% yields, respectively. Formation of the acetonide of the diol of **13** gave the benzoate **14** in 84% yield. In order to try and reproduce exactly the known Wacker oxidation, this benzoate was hydrolyzed to the alcohol **15** in 66% yield and then coupled with *p*-methoxybenzyl chloride to form the ether **16** in 55% yield. However, in our hands, the Wacker oxidation[14] of this alkene gave only a low yield of a compound which appeared to be the aldehyde **17** although its structure was never proven through characterization. This route was therefore abandoned due to the number of low-yielding and irreproducible steps.



Scheme 3. (a) PhCOOH, $Ti(OiPr)_4$, CH_2Cl_2, 18 h, 19% **12**, 32% **13**; (b) $Me_2C(OMe)_2$, TsOH, DMF, 84%;(c) MeOH, NaOH, 1 h, 66%; (d) NaH, THF, MPMCl, 55%; (e) $PdCl_2$, CuCl, DMF/H_2O, O_2, low yield.

A much more successful pathway (Scheme 4) involved first protecting the epoxyalcohol **7** as the benzyl ether **18** before adding the oxygen nucleophile.[18] Payne rearrangement is avoided by addition of sodium hydride to a mixture containing benzyl bromide, tetrabutylammonium iodide catalyst, and the alcohol **7** at -20°C to furnish the epoxy ether **18** in 79% yield. Treatment of the epoxide **18** with sodium benzylate in benzyl alcohol at 78°C furnished the alcohol **19** in 85% yield, with none of the primary alcohol isomer isolated. Protection of the remaining hydroxyl group gave the tris-benzyl ether **20** in 89% yield. Since the Wacker oxidation of similar compounds had proceeded poorly, we decided to use a hydroboration/oxidation and subsequent further oxidation to convert the alkene **20** into the desired aldehyde. Treatment with borane·THF and oxidative workup gave the alcohol **21** in 73% yield, along with the isomeric alcohol **22** (as a 4:1 mixture of diastereomers) in a surprisingly high yield of 20%. For example, Brown reported a 94:6 ratio for the hydroboration/oxidation of 1-hexene with borane·THF.[19] The structure of the

secondary alcohol **22** was confirmed by oxidation and identification of the resulting structure as the methyl ketone **24**. A Swern oxidation of the alcohol **21** gave in 93% yield the aldehyde **23** which is a protected 2-deoxy-L-ribose. Its ^{13}C NMR matched that of the benzylated 2-deoxy-D-ribose previously produced.[20] Final deprotection of the benzyl ethers of **23** with hydrogen and palladium on carbon gave no isolable products. However, using palladium hydroxide on carbon in ethanol/cyclohexene[21] and refluxing for 6 h gave a mixture of the three ethyl 2-deoxy-L-ribosides **2abc** in a 2:2:1 ratio.[22,23] We assume that the desired product 2-deoxy-L-ribose **1** was formed by debenzylation and then cyclized to the ethyl L-ribosides **2abc** under the reaction conditions.[24]



Scheme 4. (a) BnBr, Bu_4NI, NaH, THF, -20 °C → 21 °C, 3 h, 79%; (b) BnOH, NaH, 78 °C, 16 h, 85%; (c) NaH, BnBr, Bu_4NI, THF, 0 °C → 21 °C, 18 h, 89%; (d) i. BH_3·THF, THF, 6 h, ii. NaOH, H_2O_2, 50 °C, 1 h, 73% **21**, 20% **22**; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C → 21 °C, 1 h, 93%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C → 21 °C, 1 h, 74%; (g) $Pd(OH)_2$/C, EtOH, cyclohexene, 6 h, 59%, ratio of **2a:2b:2c** = 2:2:1.

Thus we have realized a short synthesis of a mixture of ethyl 2-deoxy-L-ribosides **2abc** in seven steps and in 12% overall yield from the readily available diol **6**. The key step involves the addition of sodium benzylate to the terminal end of the epoxide **18** in 79% yield. Further work on the synthesis and use of L-carbohydrates is underway.

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References and Notes

1) Presented at the 2nd Asian Federation of Medicinal Chemistry Conference (AIMECS 97), Seoul, Korea, 8/97.
2) American Chemical Society Arthur C. Cope Scholar, 1995.
3) a) Natural Sciences and Engineering Research Council (NSERC) of Canada Scholar, 1992-96. b) Departmental Awardee for Excellence during the First Year of Graduate Study, UCLA, 1993. c) Gregory Award Recipient for Excellence in Research, UCLA, 1995.
4) a) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780. b) Schinazi, R. F.; Gosselin, G.; Faraj, A.; Korba, B. E.; Liotta, D. C.; Chu, C. K.; Mathé, C.; Imbach, J.-L.; Sommadossi, J.-P. *Antimicrob. Agents Chemother.* **1994**, *38*, 2172. c) Gosselin, G.; Mathé, C.; Bergogne, M.-C.; Aubertin, A.-M.; Kirn, A.; Schinazi, R. F.; Sommadossi, J.-P.; Imbach, J.-L. *C. R. Acad. Sci. Paris Sci. Vie* **1994**, *317*, 85. d) Chu, C. K.; Ma, T.; Shanmuganathan, K.; Wang, C.; Xiang, Y.; Pai, S. B.; Yao, G.-Q.; Sommadossi, J.-P.; Cheng, Y.-C. *Antimicrob. Agents Chemother.* **1995**, *39*, 979. e) Chamberlain, S. D.; Chan, J. H.; Tidwell, J. H.; Peckham, G. E.; Harvey, R. J.; Dornsife, R. E.; Frick, L. W.; Townsend, L. B.; Drach, J. C.; Koszalka, G. W., 213th national ACS meeting, CARB 22, San Francisco, April 1997, and references in all of the above.
5) Spadari, S.; Maga, G.; Focher, F.; Ciarrocchi, G.; Manservigi, R.; Arcamone, F.; Capobianco, M.; Carcuro, A.; Colonna, F.; Iotti, S.; Garbesi, A. *J. Med. Chem.* **1992**, *35*, 4214.
6) a) Chang, C.-N.; Doong, S.-L.; Zhou, J. H.; Beach, J. W.; Jeong, L. S.; Chu, C. K.; Tsai, C.-h.; Cheng, Y.-c. *J. Biol. Chem.* **1992**, *267*, 13938. b) Chang, C.-N.; Skalski, V.; Zhou, J. H.; Cheng, Y-.c. *J. Biol. Chem.*

1992, *267*, 22414. c) Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Coong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217. d) Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202. e) Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L-.S.; Beach, J. W.; Choi, W.-B.; Yeola, S.; Liotta, D. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 672.

7) a) Hoong, L. K.; Strange, L. E.; Liotta, D. C.; Koszalka, G. W.; Burns, C. L.; Schinazi, R. F. *J. Org. Chem.* **1992**, *57*, 5563. b) Furman, P. A.; Davis, M.; Liotta, D. C.; Paff, M.; Frick, L. W.; Nelson, D. J.; Dornsife, R. E.; Wurster, J. A.; Wilson, L. J.; Fyfe, J. A.; Tuttle, J. V.; Miller, W. H.; Conderay, L.; Averett, D. R.; Schinazi, R. F.; Painter, G. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 2686.

8) a) Mansuri, M. M.; Farina, V.; Starrett, Jr., J. E.; Benigni, D. A.; Brankovan, V.; Martin, J. C. *Bioorg. & Med. Chem. Lett.* **1991**, *1*, 65. b) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Pai, B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1994**, *37*, 798. c) Gosselin, G.; Schinazi, R. F.; Sommadossi, J.-P.; Mathé, C.; Bergogne, M.-C.; Aubertin, A.-M.; Kirn, A.; Imbach, J.-L. *Antimicrob. Agents Chemother.* **1994**, *38*, 1292.

9) For leading references, see: a) L-DNA: Damha, M. J.; Giannaris, P. A.; Marfey, P. *Biochemistry* **1994**, *33*, 7877. Hashimoto, Y.; Iwanami, N.; Fujimori, S.; Shudo, K. *J. Am. Chem. Soc.* **1993**, *115*, 9883. Fujimori, S.; Shudo, K.; Hashimoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7436. b) L-RNA: Ashley, G. W. *J. Am. Chem. Soc.* **1992**, *114*, 9731.

10) a) Meisenheimer, J.; Jung, H. *Chem. Ber.* **1927**, *60*, 1462. b) Deriaz, R. E.; Overend, W. G.; Stacey, M.; Teece, E. G.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 1879. c) Holy, A. *Collect. Czech. Chem. Commun.* **1972**, *37*, 4072. d) Holy, A. *Collect. Czech. Chem. Commun.* **1973**, *38*, 423. e) Holy, A.; Sorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3383. f) Gakhokidze, R. A.; Sidamonidze, N. N. *J. Org. Chem. USSR* **1987**, *23*, 1017. g) Jung, M. E.; Xu, Y. *Tetrahedron Lett.* **1997**, *38*, 4199. h) Kim, K. S.; Ahn, Y. H.; Hurh, E. Y.; Lee, E. J. *J. Korean Chem. Soc.* **1994**, *38*, 783.

11) a) Visser, G. M.; van Westrenen, J.; van Boeckel, C. A. A.; van Boom, J. H., *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 528. b) Abe, Y.; Takizawa, T.; Kunieda, T. *Chem. Pharm. Bull.* **1980**, *28*, 1324. c) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116. d) Wulff, G.; Hansen, A. *Carbohydr. Res.* **1987**, *164*, 123.

12) a) Makin, S. M.; Raifel'd, Y. E.; Zil'berg, L. L.; Arshava, B. M. *J. Org. Chem. USSR* **1984**, *20*, 189. b) Makin, S. M.; Kruglikova, R. I.; Shavrygina, O. A.; Chernyshev, A. I.; Popova, T. P.; Nguyen, F. T. *J. Org. Chem. USSR* **1982**, *18*, 250. c) Makin, S. M.; Kruglikova, R. I.; Popova, T. P.; Chernyshev, A. I. *J. Org. Chem. USSR* **1982**, *18*, 834. d) For another use of this starting material in the synthesis of modified nucleosides with antiviral activity, see: Jung, M. E.; Gardiner, J. M. *J. Org. Chem.* **1991**, *56*, 2614; Jung, M. E.; Castro, C.; Gardiner, J. M. *Tetrahedron Lett.* **1991**, *32*, 5717; Jung, M. E.; Gardiner, J. M. *Tetrahedron Lett.* **1992**, *33*, 3841.

13) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.

14) Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678.

15) Prepared from ethyl formate by addition of vinylmagnesium bromide. Ramsden, H. E.; Leebrick, L. R.; Rosenberg, S. D.; Miller, E. H.; Walburn, J. J.; Balint, A. E.; Cserr, R. *J. Org. Chem.* **1957**, *22*, 1602.

16) a) Hatakeyama, S.; Sakurai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. b) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. c) Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5971. d) Jäger, V.; Schröter, D.; Koppenhoffer, B. *Tetrahedron* **1991**, *47*, 2195.

17) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

18) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050.

19) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.

20) Park, H. M.; Piatak, D. M.; Peterson, J. R.; Clark, A. M. *Can. J. Chem.* **1992**, *70*, 1662.

21) Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221.

22) The identity of the stereoisomers was determined by comparison of their ^{1}H and ^{13}C NMR data with that for the known methyl 2-deoxy-2-methyl-D-ribopyranoside (Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron: Asymmetry* **1996**, *7*, 779) and furanosides (Arshava, B. M.; Raifel'd, Y. E.; Makin, S. M. *J. Org. Chem. USSR* **1990**, *26*, 666 (*Zh. Org. Khim.* **1990**, *26*, 778). The structure of the pyranoside is assigned as the β-anomer since treatment of 2-deoxy-D-ribose with methanol and acid is known to form the β-anomer in preference to the α in a 9:1 ratio (Jandu, K. S.; Selwood, D. L. *J. Org. Chem.* **1995**, *60*, 5170).

23) Another run under similar conditions with only 2 h at reflux resulted in the same products **2abc** in a 2:1:1 ratio.

24) Treatment of the aldehyde **23** under the same conditions using water in place of ethanol resulted in a low yield of a compound whose NMR matched that of natural 2-deoxy-D-ribose and therefore was presumably **1**. However, it could not be isolated in good yield by this route.